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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Merchant & Gould P.C.
P.O Box 2903
Minneapolis, MN 55402-0903

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,093	GUENTHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9-3-04, 10-13-04 and 2-3-05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-50 and 53-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-50 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Contrary to applicants' summary of the claims and the amendments filed 9-3-04, 10-13-04 and 2-3-05, claims 1-38, 51 and 52 have been canceled.

An amendment was filed in 09/883093 after final on 9-3-04 but no advisory was sent. Applicants filed for RCE on 10-13-04 (with errors) and 2-3-05 (correctly). The only changes to the claims were made on 9-3-04, i.e. claim 39 was amended to the mCAR2 gene, claims 51 and 52 were canceled.

Claims 1-38, 51 and 52 are canceled. claims 53-57 have been added. Claims 39-50 and 53-57 are pending and under consideration in the instant office action.

Applicant's arguments filed 10-13-04 and 3-22-04 have been fully considered but they are not persuasive. The bulk of applicants' arguments are in the response filed 10-13-04.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The application numbers on pg 10, line 17, will have to be updated to indicate the application has bee converted to a provisional application.

Claim Rejections - 35 USC § 101

Claims 39-50 remain rejected and claims 53-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 39-50 and 53-57 are directed toward a transgenic mouse whose genome comprises a homozygous disruption in a gene encoding mCAR2, wherein as a result of the disruption, the transgenic mouse lacks production of functional protein encoded by said gene and exhibits, relative to a wild-type mouse, impaired coordination or balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality.

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf

> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

> "Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

The mCAR2 gene

"An additional member of this superfamily, constitutive activator of retinoid acid response (CAR) receptors, has been described (See, e.g. , U.S. 5,756,448). It has been suggested that CAR could play an important role in the regulatory network that controls expression of RA responsive genes. Recently. a new murine orphan member, termed mCAR was identified which is closely' related to the previously identified human orphan CAR (hCAR) (See e.g., Choi, et al., J. Biol. Chem. 272(38)23565-71(1997)). Like hCAR, mCAR expression is highest in the liver. Both mCAR 1 and hCAR are apparently constitutive transcriptional activators. This activity is dependent on the presence of the conserved C-terminal AF-2 transcriptional activation motif. As expected from its inability to bind DNA, the mCAR2 variant neither transactivates by itself nor inhibits transactivation by hCAR or mCAR1" (paragraph bridging pg 1-2).

The art did not teach the function of the mCAR2. One of skill would not have reasonably implied that mCAR2 disruptions were associated with any disease at the time of filing.

The specification teaches making mCAR2 -/+ and -/- mice with a deletion of bp 282-403 (121 bp) of the mCAR2 gene (pg 51-52; Example 1; Fig. 2). It is noted that the specification does not teach what promoters drive the LacZ and neo genes inserted into the mCAR2 gene, that the 121 bp from 282-403 provide the function of mCAR2 or that a mCAR2 gene having the 121 bp deletion produces a non-functional mCAR2 protein.

The specification suggests doing expression analysis using the mice pg 53, line 23. RNA transcripts were detectable in the liver, gallbladder, adrenal gland, small intestine and cecum (pg 53, lines 23-29). Using the mice claimed for expression analysis is not a substantial utility because many tissues expressed the transgene and because the results did not reveal the function of the mCAR2 gene.

The specification suggests using the mice as a model of disease, specifically as a model for infertility, glucose metabolism, diabetes, behavioral, neurological, neuropsychological, psychotic phenotypes (pg 18-20; pg 20, line 2). However, the specification does not disclose that neurological, neuropsychological or psychotic disease found in humans is linked to a disruption in the nuclear hormone receptor of SEQ ID NO:1. The mice had abnormalities in the spleen, thymus and lymph nodes (pg 52-53); however, the specification does not teach how to use such mice as a model of disease. The mice showed decreased performance in the rotarod test. However, the

specification does not teach how to use such mice as a model of any disease or that a disruption in SEQ ID NO:1 in humans relates to a disease that causes decreased coordination. None of the phenotypes found by the tests correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SEQ ID NO:1. The results of the behavioral tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate nuclear hormone receptor expression because nuclear hormone receptor is not expressed in the cells of the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having the phenotypes recited in claims 39-50.

The medical profession does not treat organs having decreased size or weight; therefore, treating organ size or weight is not a substantial or credible utility. Nor are organs having decreased size or weight specific to any disease; therefore, treating organ size is not a specific utility.

The medical profession does not treat organ to body weight ratio; therefore, treating organ to body weight ratio is not a substantial or credible utility. Nor is organ to

body weight ratio specific to any disease; therefore, treating organ to body weight ratio is not a specific utility.

The medical profession does not treat spleens, thymuses or lymph nodes having lymphoid depletion; therefore, treating spleens, thymuses or lymph nodes having lymphoid depletion is not a substantial or credible utility. Nor are spleens, thymuses or lymph nodes having lymphoid depletion specific to any disease; therefore, treating organ size is not a specific utility. While patients having decreased lymphoid cells are treated as a whole, the spleens, thymuses and lymph nodes are not specifically treated; therefore, targeting the increase of lymphoid cells to spleens, thymuses or lymph nodes is not credible.

The asserted utilities for a mouse having impaired coordination are not specific, substantial or credible. First, the medical profession does not specifically treat impaired coordination. For example, impaired coordination in the elderly may occur and may be caused by osteoporotic bones, symptoms of pain, or atrophied muscles. The osteoporotic bones, symptoms of pain or atrophied muscles would be treated, not the impaired coordination. Furthermore, "impaired coordination" is a relative term. Second, the medical profession does not treat clumsiness. For example, a first tennis player may have impaired coordination, or lower than average coordination (clumsy), while the second tennis player has better than average coordination. The specification does not teach how to treat the first player so that the first player would be as coordinated as the second player. Treating clumsiness cannot be envisioned; therefore, using the mouse as a model for clumsiness is not a substantial or credible utility. In addition, the rotarod

test used to determine impaired coordination is used to test gross neurological function; therefore, using mice with impaired coordination is not specific to any neurological condition. Overall, mice having impaired coordination do not have a specific, substantial or credible.

In addition, a mouse having a small or light thymus, spleen, lymph node is not specific to any disease condition. A mouse having decreased coordination/balance is not specific to any disease. A disruption in a mCAR2 gene has not been linked to any disease condition. Therefore, the mice are not models of any disease.

Wild-type mice could be used to determine agents that make organs bigger or heavier. Wild-type mice could be used to determine agents that improve coordination. Therefore, using mice to find agents that increase organ size/weight or coordination/balance is not specific to mice having a disruption in the mCAR2 gene as claimed. In addition, the specification does not teach identifying any therapeutic agents using the mice; therefore, applicants' assertion is not credible in view of the teachings in the art and the lack of examples in the specification.

The data provided in the specification is not substantial because the observed phenotypes may have been a result of the donating ES cell phenotype and cannot be compared to a C57Bl6 wild-type control mouse. The Jackson Laboratory describes C57BL/6 mice as having a high susceptibility to diet-induced obesity and type 2 diabetes (see www.jax.com under "Description of mouse strains," stock number 000664). The mice in the examples of the specification were of a mixed strain (F2 homozygotes were 75% C57Bl/6 and 25% 129/OlaHsd). The specification does not

teach which generation of mice were tested or to what wild-type control they were compared. If the homozygous F2 mice were compared to a C57Bl/6 wild-type control, the phenotype of the 129/0laHsd strain may have contributed to the observed difference in the phenotype and not the disruption of the mCAR2 gene. Crabbe of record supports the examiners position by teaching that C57Bl/6 mice have different phenotypes than other strains of mice (Science, June 4, 1999, Vol. 284, pg 1670-1672). Therefore, a mixed strain knockout mouse may have a phenotype that is found in the contributing ES cell strain and not in the wild-type C57Bl6 mouse. The specification does not teach the mixed strain knockout mouse was backcrossed adequately for a proper comparison to a wild-type C57Bl6 mouse. The specification does not teach the mixed strain knockout mouse was backcrossed adequately for a proper comparison to a wild-type C57Bl6 mouse. The specification does not teach that both wild-type C57Bl/6 and the wild-type contributing ES cell strain had the same body weight. As such, one of skill would not be able to conclude that the observed difference was attributed to the knockout of mCAR2 and not the 129/OlaHsd genotype of the ES cell strain contributing to the genome of the heterozygous mice. Thus, the mice claimed do not have substantial utility because the data provided is not substantial.

The specification asserts the mice claimed are used as a model of disease relating to disruptions in mCAR2. The asserted utility is not substantial, specific or credible because the phenotypes claimed do not reflect a disease state in humans. No diseases in humans are caused by a disruption in mCAR2. Therefore, the asserted utility of using the mouse as a model of disease is not substantial or specific.

The specification asserts the mice claimed are used to determine compounds that modulate mCAR2 expression. The asserted utility is not credible because mCAR2 is not expressed in the mice and because compounds found using such a mouse may act on non-mCAR2 proteins in a pathway related to mCAR2.

The specification asserts the mice claimed are used to determine compounds that ameliorate a particular phenotype. The asserted utility is not specific, substantial or credible for reasons in the following paragraphs.

Determining compounds that ameliorate a phenotype is not a specific utility because the specification does not link any of the phenotypes described in the specification to any specific disease or to a disease caused by a mCAR2 disruption in humans.

In fact, the phenotypes observed in the Examples may be a result of other genes compensating for the disruption of mCAR2. Olsen taught that a disruption of a gene in a mouse does not necessarily correlate to or cause the phenotype observed in the mouse because other proteins compensate for the disruption (Olsen, GABA in the Nervous System, 2000, pg 81-95; "This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products" pg 82, last 11 lines of col. 1). Therefore, determining compounds that ameliorate the phenotypes observed in the Examples would not be a specific or substantial utility because the phenotypes observed in the Examples are not necessarily caused by the disruption of mCAR2.

For example, Srivastava (PNAS, Nov. 23, 1999, Vol. 96, No. 24, pg 13783-13788) taught making an ANX7 -/- mouse with defects in insulin secretion and that the observed phenotype was a result of compensation by making more secreting cells and loading each secretory granule with more insulin" (pg 13788, last full ¶). Therefore, observed phenotypes in the instant application may be a result of cells compensating for the lack of mCAR2 and not a result of the disruption of the mCAR2 gene.

Determining compounds that ameliorate a phenotype is not a credible utility because the specification does not identify any compounds that alter a phenotype of the mice.

Determining compounds that ameliorate a phenotype is not a specific or substantial utility because determining compounds that alter a phenotype may not reveal the function of the protein. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-13). Thus, knockout mice may be used to identify compounds that bind to the knocked out gene ($GABA_B$ in the case of Bowery), but the identification of such compounds may not reveal the function of the protein (because Bowery identified agents that altered phenotypes but the functional properties of GABA subunits remained unknown).

Determining compounds that ameliorate a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not mCAR2 itself. Determining compounds that ameliorate a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. As such, determining compounds that ameliorate a phenotype is not a specific or substantial utility.

Determining compounds that ameliorate a phenotype is not a substantial utility because compounds that alter a phenotype may not be therapeutic in humans. MacDonald (J. Biol. Chem., Nov. 22, 2002, Vol. 277, pg 44938-44945) identified a bispidine derivative (C-1) that antagonized Kv2.1 using different mouse cells, but taught that further experimentation was required to determine how to use bispidine derivatives to treat diabetes (see last ¶). Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) administered antagonists of $GABA_B$ receptor to $GABA_B$ -/- knockout mice, which caused decreased anxiety in various tests. While the antagonists were not found using the mice, they were found using *in vitro* assays (see pg 1058, col. 2, 1st full ¶, lines 4-8, and Urwyler *et al,* 2003, referred to therein). Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate

pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). However, the art did not and does not teach using the antagonist to treat any disease. Thus, compounds that alter a phenotype in knockout mice may not be used for therapy in humans. Using the mouse to obtain clues of the role of the $GABA_B$ receptor in a molecular pathway of anxiety as taught by Mombereau or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of $GABA_B$ in the pathway. Too much further research would be required to determine whether "positive modulators" or "antagonists" that bind $GABA_B$ will treat anxiety or how to modify the compounds so that they can treat anxiety. Further research would be required to determine how to use agents identified using the mouse to treat disease, which is not a "substantial utility" (see Utility Guidelines under "substantial utility" - methods of determining a compound that itself has no "specific and/or substantial utility"). Therefore, determining agents that modulate the phenotype of a knockout mouse is not a substantial utility because the agent may only provide clues to the function of the knocked out gene and may not be capable of treating disease in humans.

Knockout -/- or -/+ mCAR2 mice did not have a "well-known utility" to study the function of mCAR2. MPEP 2701 II(A)(3) requires a "well-established utility" must be a

utility that is specific, substantial and credible. It was well known that knockout mice could be used for scientific research to study the function of a gene. However, scientific research is not the same as "patentable utility" or a "well-established" utility.

Olsen (GABA in the Nervous System, 2000, pg 81-95, also cited above) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to determine the function of the gene. In fact, the function of the gene may never be determined from the knockout mouse. A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-

established utility." Using the mouse for further research is not a substantial utility, which is specifically described in the utility guidelines:

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study would have been required to determine how to use the -/- or -/+ mCAR2 mouse known in the art or of applicants' invention to determine the function of the gene. The overall phenotype of the applicants' mice does not correlate to Dent Disease or any other disorder. Therefore, further study would be required to determine the function of the mCAR2 gene or how to use the mice as a model for any disease. As such, using the mice claimed to determine the function of the mCAR2 is not a "substantial utility."

Applicants argue the claimed invention has a well-established utility because a person of ordinary skill would immediately appreciate why the knockout mice were useful to define the function and role of the disrupted gene. Applicants' argument is not persuasive.

MPEP 2701 II(A)(3) requires a "well-established utility" must be a utility that is specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to

determine the function of the gene using the mouse. In fact, the function of the gene may never be determined from the knockout mouse. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility" (see utility guidelines, "[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved"). In this case, the results of such further study may never reveal the function of the TMEM3 gene and least significant further study would have been required to use the knockout mice to determine the function of the TMEM3 gene.

Applicants point to an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-924), The Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) and Gene VII (Lewin, Oxford University Press (2000)) to establish the mice had "well-established" utility (pg 4-8 of response). Applicants' arguments are not persuasive.

First, the NIH report and Austin were not available until 2004 and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, one mouse with lipoma or mice with increased pain sensitivity as claimed are not models of any disease because they are not symptoms of disease.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. None of references teach the mice will determine the function of the gene. Applicants have used the mice in expression analysis and phenotype analysis tests, but applicants have not determined the function of the gene. Simply using the mice for further research of the mCAR2 gene is not a specific or substantial utility. None of the references teach a specific or substantial utility for mice with a disruption in the mCAR2 gene as claimed.

Applicants cite Crabbe of record who taught "[t]argeted and chemically induced mutations in mice are valuable tools in biomedical research." Applicants argue Luo (J. Steroid Biochem. Mol. Biol. 1999, Vol. 69, No. 1-6, pg 13-18) taught knockout mice were used in the art for studying the function of orphan

nuclear hormone receptors. Applicants also refer to Choi (1994). Applicants' arguments are not persuasive. Luo and Choi (1994) not been provided and cannot be considered in full. However, while knockout mice were used for research in the art at the time of filing, it was well known that such mice did not necessarily provide the function of the gene (see references cited by the examiner above and Luo cited by applicants). A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a patentable, "well-established utility." Upon reading the citation of Luo provided by applicants, it appears that Luo did not determine the function of the receptor or determine compounds capable of treating disease using the mice. While Choi determined HNF-4 (an orphan receptor) in the visceral endoderm is essential for embryonic development and normal gastrulation, Choi did not determine the specific function of HNF-4 within the realm of development or gastrulation. Merely gaining clues about the function of a gene using knockout mice does not rise to the level of a substantial utility.

Applicants argue the data obtained from the mice has been subscribed to by at least three pharmaceutical companies; therefore, applicants conclude that those of skill would recognize the utility of the mice (pg 9). Applicants' argument is not persuasive. Sales may be evidence to overcome a 103 obviousness rejection, but there is no case law that establishes that "sales" are evidence of patentable utility. Evidence of sales is not evidence the mice have a "well-established" utility or a "specific utility" or a "credible utility."

Applicants argue the 103 contradicts the utility rejection (¶ bridging pg 9-10). Applicants' argument is not persuasive. The examiner has provided adequate reasoning to support both the 101 and 103 rejections. The desire of those of ordinary skill to gain clues as to the function of genes was well established at the time of filing. The fact that those of ordinary skill in the art desired to make knockout mice to gain clues as to the function of genes does not necessarily mean the mice would have a specific and substantial utility, i.e. that those of ordinary skill would determine the function of the gene from the clues provided by the mice. Evidence is provided by applicants who used the mice in various tests and gained clues regarding the gene but did not teach the function of the gene.

Applicants are reminded that In re Schoenwald, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. In this case, the mouse claimed might only provide a clue to a developmental process or signal transduction pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO:1 is involved in development or signal transduction pathway. The phenotype provides only a clue that SEQ ID NO:1 is generically involved in development or a signal transduction pathway influenced by numerous proteins.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure for mice with the phenotype described (pg 10). Applicants cite Austin (cited above) who teach knockout mice are widely

accepted models and the utility of these mice would be readily apparent to those of skill in the art (pg 11-12 of response). Applicants' arguments are not persuasive. Not all claims are limited to mice with a phenotype. Mice with decreased performance in a rotarod test, decreased spleen size, reduced spleen to body weight ratio, lymphoid depletion of the spleen, thymus size/weight, etc. do not correlate to any diseases. The examiner has provided ample reasoning and evidence why those of skill in the art at the time of filing would doubt why each phenotype fails to have substantial utility. The examiner has provided ample reasoning why each asserted utility fails to have substantial and/or specific utility. Even applicants' own further research, i.e. the expression, physical and behavioral analysis did not reveal the function of the mCAR2 gene. Significant further research in this case is required to use the mice with the phenotypes described to determine the function of the mCAR2 gene. Therefore, using the mice with the phenotypes described to determine clues to the function of the mCAR2 gene does not constitute a patentable utility.

Claim Rejections - 35 USC § 112

Enablement

Claims 39-50 remain rejected and claims 53-57 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having abnormal pain threshold for reasons of record.

New Matter

Claims 39-50 and claims 53-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "a gene encoding mCAR2" in claim 39 is new matter. Pg 6, lines 24-29, describes a "nuclear hormone receptor gene" as being the sequence of SEQ ID NO:1 or the isoform mCAR2 in Genebank Accession No.: AF009328; GI NO: 2267577. Nowhere does the specification refer to the genus mCAR. The specification only contemplates the species of SEQ ID NO:1 within the genus "mCAR2." The specification does not contemplate the broad genus of any mCAR2 gene or teach any other mCAR2 sequences.

The phrase "null endogenous mCAR2 allele" in claim 53 is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The phrases "null allele" and "mCAR2 allele" cannot be found and raise indefinite rejections (see 112/2nd below).

A "null endogenous mCAR2 allele... ...comprising exogenous DNA" in claim 53 is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The specification does not contemplate introducing any "exogenous DNA" as broadly claimed to disrupt the mCAR2 gene.

The breadth of "selection marker" in claim 56 is new matter. Support cannot be found in the specification or claims as originally filed.

Indefiniteness

Claims 39-50 remain and claims 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The metes and bounds of what applicants' consider "a gene encoding mCAR2" in claim 39 cannot be determined. The specification defines a nuclear hormone receptor gene as "a sequence comprising SEQ ID NO: 1 or comprising the sequence encoding the orphan nuclear hormone receptor isoform mCAR2 identified in Genebank as Accession No.: AF009328, GI: NO: 2267577. In one aspect, the coding sequence of the nuclear hormone receptor gene comprises SEQ ID NO:1 or comprises the nuclear hormone receptor gene identified in Genebank as Accession No.: A17009328; GI: NO: 2267577" (pg 6, lines 24-29). However, it cannot be determined how much homology is required for a sequence to still be considered an "orthologue" or "homolog" thereof and still be a mCAR2 gene. As such, the metes and bounds of genes that meet applicants' definition of a nuclear hormone receptor gene cannot be determined. Applicants do not define mCAR2 genes. Therefore, it is unclear if an mCAR2 gene is limited the SEQ ID NO:1, to any CAR2 gene or to any nuclear hormone receptor as broadly defined in the specification.

The metes and bounds of a "mCAR2 allele" in new claim 53 are indefinite for

reasons in the paragraph above.

The metes and bounds of a "null mCAR2 allele" in claim 53 are indefinite. It is unclear if the phrase is limited to a mouse without any of the mCAR2 gene, or if the phrase encompasses a mouse without any of the coding region of the mCAR2 gene, a mouse with a disruption in the mCAR2 gene, wherein said disruption does not allow production of functional mCAR2, or a mouse with a disruption in the mCAR2 gene, wherein said disruption causes less than normal amounts of functional mCAR2. The metes and bounds of what applicants consider a "null" allele cannot be determined.

Claims 39 and 41-50 are indefinite because the metes and bounds of what applicants consider an "abnormality" cannot be determined. The term "abnormal" is subjective and is not defined in the specification and is a subjective term in the art.

Claim Rejections - 35 USC § 102

In the previous office action, the examiner withdrew the rejection over Kato because the nuclear hormone receptor gene VDR is not a mCAR gene as claimed because the nuclear hormone receptor described in the specification is limited to SEQ ID NO:1 or encompasses SEQ ID NO:1 and the orphan nuclear hormone receptor isoform mCAR2 identified in Genebank as Accession No.: AF009328, GI NO: 2267577. upon reconsideration of the breadth of genes encompassed by the mCAR gene as claimed, the rejection has been revived.

Claims 39-50 and 53-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato (J. Biochem., May 2000, Vol. 127, pg 717-722) supported by Li (PNAS, Sept. 1997, Vol. 94, pg 9831-9835).

Kato taught heterozygous and homozygous mice having a disruption in the nuclear hormone receptor gene VDR. The VDR gene is an mCAR2 gene as claimed because it meets the definition of nuclear hormone receptor genes in the specification, i.e. it shares homology with SEQ ID NO:1. Li was cited by Kato in the first sentence of the paragraph bridging pg 718-719 (26) and supports the fact that the disruption was inherently made using the neomycin resistant gene (pg 9831, col. 2, "Generation of VDR Null Mice"; "...16 of which had a single copy of the neomycin resistance gene." Claims 39-50 are included because the metes and bounds of "abnormalities" are unclear. Without evidence to the contrary, the mice taught by Kato inherently had the "abnormalities" claimed because they had bone and parathyroid abnormalities, hair loss and increased immunoreactive PTH levels (See Li, ¶ bridging pg 9832-9833).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato (J. Biochem., May 2000, Vol. 127, pg 717-722) supported by Li (PNAS, Sept. 1997, Vol. 94, pg 9831-9835) in view of Choi (J. Biol. Chem., 1997, Vol. 272, pg 23565-23571).

Kato taught heterozygous and homozygous mice having a disruption in the nuclear hormone receptor gene VDR. The VDR gene is an mCAR2 gene as claimed because it meets the definition of nuclear hormone receptor genes in the specification, i.e. it shares homology with SEQ ID NO:1. Li was cited by Kato in the first sentence of the paragraph bridging pg 718-719 (26) and supports the fact that the disruption was

inherently made using the neomycin resistant gene (pg 9831, col. 2, "Generation of VDR Null Mice"; "...16 of which had a single copy of the neomycin resistance gene." Kato did not teach disrupting SEQ ID NO:1. Claims 39-50 are included because the metes and bounds of "abnormalities" are unclear. Without evidence to the contrary, the mice taught by Kato inherently had the "abnormalities" claimed because they had bone and parathyroid abnormalities, hair loss and increased immunoreactive PTH levels (See Li, ¶ bridging pg 9832-9833).

However, Choi taught the nucleic acid sequence of the mouse nuclear hormone receptor gene of SEQ ID NO:1.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in an nuclear hormone receptor gene as taught by Kato wherein the gene was the nuclear hormone receptor of SEQ ID NO:1 taught by Choi. One of ordinary skill in the ad at the time the invention was made would have been motivated to disrupt SEQ ID NO:1 instead of the VDR nuclear hormone receptor gene taught by Kato to gain clues to the function of SEQ ID NO:1 in vivo.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has. been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER